IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	**Confirmation No. 8747**
Norihito SHIMONO et al.	:	Docket No. 2002_0055A
Serial No. 10/048,063	:	Group Art Unit 1615
Filed January 28, 2002	:	Examiner Micah Paul Young

SOLID PREPARATION CONTAINING CHITOSAN
POWDER AND PROCESS FOR PRODUCING THE SAME

REQUEST FOR RECONSIDERATION

Commissioner for Patents
P.O. Box 1450
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Sir:

This is responsive to the Official Action dated December 17, 2003, the time for responding thereto being extended for two months in accordance with a petition for extension submitted concurrently herewith.

Favorable reconsideration is respectfully requested in view of the following remarks.

Claim 17 is rejected under 35 USC 112, second paragraph, as being indefinite on the basis that it is inconsistent and redundant with respect to claim 7. This ground of rejection is respectfully traversed.

The basis of the rejection appears to be the Examiner's misunderstanding that claim 7 is directed to an enterically coated dosage form. However, claim 7 does not require an enteric coating.

Thus, it is respectfully submitted that claim 17 is not inconsistent or redundant with respect to claim 7.

Reconsideration is respectfully requested.

Claims 1, 5, 6, 7, 9, 10, 16 and 17 are rejected under 35 USC 102 as being anticipated by Sekigawa et al., the '720 patent. This ground of rejection is respectfully traversed.

(A) The Present Invention

The present invention includes two features.

The first feature (as claimed in the product claims 1-5, 10-15, and the process claim 6) is a colonic delivery solid preparation (= an enteric preparation) having the following structure;

(i) Core - comprising a medicament-containing solid material

(ii) Inner coating layer - of a water-insoluble polymer wherein a chitosan powder is dispersed,

and (iii) Outer coating layer - of an enteric polymer.

The second feature (as claimed in the product claims 7-8, and a process claim 9) is a solid preparation (= a sustained release preparation) having the following structure:

(i) Core - comprising a medicament-containing solid material

and (ii) Single coating layer - of a water-insoluble polymer wherein a chitosan powder is dispersed.

The most important characteristic of the present invention is to coat the medicament-containing core with a chitosan powder dispersed water-insoluble polymer, whereby the preparation exhibits excellent effects in both uses.

(1) In case of the first feature, when the colonic delivery solid preparation is orally administered, the preparation passes through the stomach without change owing to the outer enteric coating layer, and the enteric coating is dissolved and removed in small intestine tract. As a result, during passing the small intestine and with dissolving and removing of the enteric coating, the medicament contained in the core is gradually released through the water-insoluble polymer in the inner coating layer.

After the solid preparation reaches the large intestine (colon), the chitosan powder dispersed within the water-insoluble polymer of the inner coating layer is specifically decomposed by *E. coli* and thereby many pores are formed in said inner coating layer. As a result, the release of medicament contained in the core is accelerated through the pores.

Thus, the preparation having an enteric coating of the first feature is prepared for the purpose of releasing the medicament more in the large intestine. When the kind and amount of the water-insoluble polymer and chitosan powder are varied, the starting point and the speed of the release of medicament can be controlled. Accordingly, the delivery of medicament can specifically be controlled with respect to the region to be released as well as the time for release, and thereby the release of medicament can be controlled in the wide range from the small intestine to the large intestine and further the rate of release is also well controlled.

(2) In the case of the second feature, when the solid preparation in the form of a sustained release preparation is orally administered, the chitosan powder dispersed within the water-insoluble polymer coating layer is partially dissolved by an acid in the stomach to give some pores in the coating layer, through which the medicament contained in the core is partly released in the stomach. Further, during passing through the small intestine, the medicament is continuously released through the pores while chitosan is no further dissolved. After the solid preparation reaches to the large intestine tract, chitosan powder is specifically decomposed by *E. coli* and thereby the medicament is released at an accelerating rate.

Thus, in the second feature, the release of medicament can also be controlled in the wide range through the gastrointestinal tracts such as the stomach, the small intestine and the large intestine in terms of the release rate and amount of the medicament.

(B) Sekigawa et al., USP 5,217,720

The invention of Sekigawa et al. is concerned with a coated solid medicament form suitable for oral administration having reliable releasability of the active ingredient only in the large intestine.

The coated solid preparation of Sekigawa et al. is composed of

(i) Core - a solid medicament form containing the active ingredient,

(ii) Inner coating layer - a coating with a chitosan having a specific degree of deacetylation and a specific degree of polymerization,

(iii) Top coating layer - a coating with a specific enteric-soluble polymer,

and further optionally,

(iv) Undercoating layer - a coating with a specific enteric-soluble polymer.

Said undercoating layer is formed by coating the core medicament form with the enteric polymer prior to coating with chitosan, which is given in order to be more reliable the releasability of the active ingredient only in the large intestine.

The specific-enteric polymers for the top coating layer (iii) and for the undercoating layer (iv) are specified in the description on col. 5, lines 2-4, and col. 5, lines 32-43, respectively.

Thus, the preparation of Sekigawa et al. having more reliable releasability of the active ingredient is a triple-coated solid medicament form. When the preparation of Sekigawa et al. is orally administered, it is not changed during passing through the stomach and the small intestine, but upon reaching to the large intestine the chitosan is specifically decomposed by *E. coli* and thereby the medicament contained in the core is released. In case of lacking the enteric undercoating layer, when the enteric top coating layer is dissolved in the small intestine, the chitosan coating layer may swell and then the medicament may be released through the swollen chitosan layer in some degree. By providing the enteric undercoating layer, the releasability only in the large intestine becomes more reliable.

(C) Differences of the preparation of the present invention from that of Sekigawa et al.

(1) The most important difference between the Sekigawa et al and the present invention is in that the medicament-containing core is coated with only chitosan in the preparation of Sekigawa et al., but on the other hand, the medicament-containing core is coated with a chitosan powder-dispersed water insoluble polymer in the preparation of the present invention.

In item 5 of the Action, the Examiner states "the chitosan is dissolved with water-insoluble polymers and spray-dried onto the solid core", referring to column 4, line 67 to column 5, line 19 of the '720 patent. However, this portion of the '720 patent is directed to the preparation of the enteric coating, not the chitosan layer.

Specifically, on lines 67-68 of column 4, the '720 patent teaches "The inventors have conducted extensive studies to find an enteric coating material to satisfy the above mentioned requirements leading to a conclusion that suitable materials include...." . In column 5, lines 6-14,

the '720 patent further teaches "For example, the cellulose derivative is dissolved in ethyl alcohol or in a mixture of ethyl alcohol and water to prepare a coating solution or a fine powder of the cellulose derivative is dispersed in water to prepare a coating dispersion and the solid core medicament form provided with the first coating layer of chitosan is coated by spraying the prepared coating solution or dispersion...".

The '720 patent at column 4, lines 7-27, teach the application of the chitosan layer. There is no disclosure or suggestion of applying chitosan with a water-insoluble polymer according to the claimed invention.

In summary, the disclosure referred to by the Examiner at column 4, line 67 to column 5, line 19 teaches application of the enteric coating layer using a water-insoluble polymer, not application of the chitosan layer.

(2) Owing to the difference in the coating layer, there is a remarkable difference in the medicament releasing property between the preparation of the present invention and that of the Sekigawa et al.

(a) That is, the chitosan-coating layer of the preparation of Sekigawa et al. is rapidly decomposed in the large intestine to denude the medicament-containing core and thereby the medicament is released very rapidly, and hence, it may have a problem in that the medicament is undesirably excessively released.

On the contrary, according to the preparation of the present invention, the chitosan powder is dispersed in the water-insoluble polymer layer, and hence, even when the chitosan is decomposed in the large intestine, the medicament will be gradually released through the pores in the water-insoluble polymer layer formed by decomposing of the dispersed chitosan powder. In addition, the release rate of the medicament can be controlled by choosing appropriately the combination of the kinds of the water-insoluble polymer and the kinds and amounts of chitosan powder.

(b) In the preparation of Sekigawa et al. there is a time lag until decomposition of the chitosan layer after reaching to the large intestine, and hence, the release of medicament is delayed. On the other hand, in the preparation of the present invention, the medicament releasing

point can advantageously be controlled by regulating the thickness of the chitosan powder-dispersed water-insoluble polymer layer. Further, since the medicament may also be released through the water-insoluble polymer layer to some extent, even though there is a time lag until decomposing the chitosan powder in the large intestine, no lag time exists in the initiation of release of medicament. In other words, the preparation of the present invention can more surely exhibit the desired release properties in comparison with the preparation of Sekigawa et al.

(c) According to the preparation of Sekigawa et al., the coating layer is composed of chitosan only, and hence, medicament can be released only after reaching to the large intestine, and hence it may be used merely for the treatment of a disease in the large intestine. On the contrary, the preparation of the present invention can control the initiation and rate of release of medicament by regulating the thickness of the coating layer with the chitosan-dispersed water-insoluble polymer.

(d) The preparation of Sekigawa et al. having the coating layer composed of only chitosan cannot exhibit a sustained release property, because when the decomposition of chitosan in the large intestine once initiates, the coating layer is rapidly decomposed and as a result the medicament is released very rapidly. On the other hand, the preparation of the present invention can show excellent sustained release property because the medicament is released gradually through the pores in the water-insoluble polymer layer and further by controlling the thickness of the coating layer with the chitosan-dispersed water-insoluble polymer.

(3) In the preparation of Sekigawa et al., the chitosan has a specific degree of deacetylation and a specific degree of polymerization and it is applied after dissolving in an acidic solution, and hence, the medicament contained in the core may affected badly by the acid remained in the acidic solution. On the other hand, in the preparation of the present invention, chitosan powder can be any conventional one and is dispersed in the water-insoluble polymer without using such an acidic solution.

The specific structure and effects of the present invention are never taught or even suggested by the cited Sekigawa et al.

Accordingly, it is respectfully submitted that the cited reference fails to teach each material feature of the rejected claims, and thus the 102 rejection should be withdrawn.

Lastly, claims 2-4, 8 and 11-15 are rejected under 35 USC 103 as being unpatentable over the '720 patent together with Suzuki et al., the '064 patent. This ground of rejection is also respectfully traversed.

As is explained above, the preparation of the present invention is clearly different from the preparation of Sekigawa et al. in the structure and the effects thereof.

The invention of the cited Suzuki et al., '064 is concerned with a large intestinal dissociative hard capsule which comprises (i) a capsule mainly composed of chitosan which is formed from a solution of the chitosan in an aqueous acetic acid solution, and (ii) a coated layer of a polymer solution in a liquid having pH of at least 5 on the surface of the capsule.

In Suzuki et al., the polymer for coating the chitosan capsule is a conventional enteric polymer (cf. Suzuki et al. '064, col. 3, lines 1-8), and the chitosan capsule is formed from a specific solution of chitosan in an aqueous 1% by weight acetic acid solution having the viscosity of not higher than 100 cps at 20°C and the deacetylation degree of the chitosan being from 60 mol % to 98 mol % (cf. Suzuki et al., '064, col. 2, lines 38-48). Thus, the invention of Suzuki et al. is characteristic in that the chitosan capsule is formed from a specific solution of chitosan in a specific aqueous acetic acid solution and is coated with a conventional enteric polymer coating.

Thus, the invention of Suzuki et al. is essentially different from the present invention in the inventive concept and also in the structure of the product.

It should be emphasized that both of the cited Sekigawa et al. and Suzuki et al. employ a water-insoluble polymer only with the enteric polymer coating. They never mention the use of water-insoluble polymer, and further never teach or even suggest a coating with a water-insoluble polymer, wherein chitosan is dispersed therein. This is the most important characteristic of the present invention. Furthermore, neither Sekigawa et al. nor Suzuki et al. teach or even suggest the excellent effects of use of said characteristic coating with a water-insoluble polymer dispersed with chitosan.

In item 9, the Examiner also alleges that the '064 patent discloses a solid medicament comprising chitosan dissolved in a water-insoluble polymer, referring to column 2, lines 38-48.

However, this passage merely mentions "the viscosity at 20°C of a solution formed by dissolving the chitosan in an aqueous 1% by weight acetic acid solution at a concentration of 1% by weight being not higher than 100 cps, and preferably from 100 cps to 3 cps and the deacetylation degree of the chitosan being from 60 mol % to 98 mol %." Thus, this passage in the '064 patent discloses merely a solution of chitosan in an aqueous 1% by weight acetic acid, but it never discloses or suggests that chitosan is dissolved in a water-insoluble polymer.

In fact, chitosan can never be dissolved in a water-insoluble polymer but can merely be dispersed in a water-insoluble polymer as disclosed in the present description.

The Examiner further points out that water-insoluble polymers include ethylcellulose, etc., referring to column 3, lines 9-55. However, such water-insoluble polymers are described in the '064 patent as being used for applying the enteric coating over the chitosan capsule of the Suzuki et al. invention. See column 3, lines 1-8 and 60-64.

In view of the foregoing, it is respectfully submitted that the cited references fail to disclose or suggest the solid preparations according to claims 1-17. Accordingly, reconsideration and allowance is respectfully solicited.

Respectfully submitted,

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